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EXAMINER	
LEE, JAE W	

ART UNIT	PAPER NUMBER
1656	

NOTIFICATION DATE	DELIVERY MODE
02/22/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/590,275	ENDO ET AL.	
	Examiner	Art Unit	
	JAE W. LEE	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 October 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10* is/are pending in the application.

4a) Of the above claim(s) *5-9* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3 and 10* is/are rejected.

7)☒ Claim(s) *4* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 August 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *08/22/2006; 07/25/2007; 05/13/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application.
6) ☐ Other: _____.

DETAILED ACTION

Application status

Claims 1-10 are pending in this application.

Priority

The instant application is the 371 national stage entry of PCT/JP2005/003756 filed on 03/04/2005 as requested in the declaration. The Examiner notes that the requirements of national stage entry of the instant application had been completed (note assigned U.S. filing date) within 30 months of the earliest claimed priority date; the related international application includes both a search report and a preliminary examination report.

Acknowledgment is made of Applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d) to a foreign patent application JAPAN 2004-062852 filed on 03/05/2004 without English translation.

Election

Applicant's election with traverse of Group I, Claims 1-4 and 10 in the response filed on 10/21/2009, is acknowledged.

Applicants argue that restriction is only proper if the claims of the restricted groups are independent or patentably distinct and there would be a serious burden placed on the Office if restriction is not required (MPEP §803). The burden is on the

Office to provide reasons and/or examples to support any conclusion in regard to patentable distinction (MPEP §803). Moreover, when citing lack of unity of invention in a national stage application, the Office has the burden of explaining why each group lacks unity with the others (MPEP § 1893.03(d)), i.e. why a single general inventive concept is nonexistent. The lack of a single inventive concept must be specifically described. Annex B of the Administrative Instructions under the PCT, paragraph b (Technical Relationship), states, emphasis added: The expression "special technical feature" is defined in Rule 13.2 as meaning those technical features that defines a contribution which each of the inventions, considered as a whole, makes over the prior art. The determination is made on the contents of the claims as interpreted in light of the description and drawings (if any). Applicants respectfully submit that the Office did not consider the contribution of each invention, as a whole, in alleging the lack of a special technical feature over the cited reference. Applicants also respectfully submit that the Office has not provided any indication that the contents of the claims interpreted in light of the description were considered in making this allegation. Therefore, the Office has not met the burden necessary to support the assertion of a lack of unity of the invention.

Applicants' arguments have been fully considered but are not deemed persuasive for the following reasons. Although Applicants allege that the Office did not consider the invention as a whole, interpreted in light of the description, the Examiner notes that the specification describes the mutant *Bacillus* bacterium as one that "is constructed such that DNA having a promoter sequence which is recognized and transcribed specifically during the sporulation stage and which is ligated to an upstream

end of a *sigA* gene or a gene equivalent thereto is present on the genome or a plasmid thereof" (see paragraph [0017] on page 8 of the specification). Furthermore, the specification states that "[n]o particular limitation is imposed on the origin of a parent microorganism employed for constructing such a mutant *Bacillus* bacterium, so long as the parent microorganism is a bacterium belonging to the genus Bacillus exhibiting a unique feature of sporulation, and a wild type microorganism or a mutant microorganism may be employed (see paragraph [0018] of the specification). Therefore, in light of the specification as previously explained, Haldenwang WG (THE SIGMA FACTORS OF BACILLUS SUBTILIS, MICROBIOLOGICALREVIEWS, AMERICAN SOCIETY FOR MICROBIOLOGY, WASHINGTON, DC, US, vol. 59, no. 1, 1 March 1995 (1995-03-01), pages 1-30, see IDS) teaches a mutant Bacillus Subtilis bacterium comprising, on the genome or plasmid thereof, DNA having [i] an mutant *lacUV5* promoter sequence (see page 4, right column, lines 29-30) or [ii] the promoter sequences P_1-P_6 being ligated to an upstream end of the *sigA* gene (see under "Regulation of the *sigA* operon" on page 5, and Figure 2) recognized and transcribed specifically during the sporulation stage, and a *sigA* gene, which anticipates the limitation of claim 1. Thus, the shared technical feature of the groups is not a "special technical feature", unity of invention between the groups does not exist. In addition, there would be a serious search and examination burden if restriction were not required because one or more of the following reasons apply: (a) the inventions have acquired a separate status in the art in view of their different classification; (b) the inventions have acquired a separate status in the art due to their recognized divergent subject matter; (c) the inventions require a different field of

search (for example, searching different classes/subclasses or electronic resources, or employing different search queries); (d) the prior art applicable to one invention would not likely be applicable to another invention; (e) the inventions are likely to raise different non-prior art issues under 35 U.S.C. 101 and/or 35 U.S.C. 112, first paragraph. For the reasons provided herein and in the previous office action mailed on 10/13/2009, the instant restriction requirement is deemed proper.

Claims 5-9 are withdrawn from further consideration by the Examiner, 37 CFR 1.142(b) as being drawn to a non-elected invention.

It is noted by the Examiner that claims 5-9 are subject to rejoinder once Claims 1-4 and 10 become allowable. The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and a product claim is subsequently found allowable, withdrawn process claims that depend from or otherwise include all the limitations of the allowable product claim will be rejoined in accordance with the provisions of MPEP § 821.04. Process claims that depend from or otherwise include all the limitations of the patentable product will be entered as a matter of right if the amendment is presented prior to final rejection or allowance, whichever is earlier. Amendments submitted after final rejection are governed by 37 CFR 1.116; amendments submitted after allowance are governed by 37 CFR 1.312.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to

be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103, and 112. Until an elected product claim is found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowed product claim will not be rejoined. See "Guidance on Treatment of Product and Process Claims in light of In re Ochiai, In re Brouwer and 35 U.S.C. § 103(b)," 1184 O.G. 86 (March 26, 1996). Additionally, in order to retain the right to rejoinder in accordance with the above policy, Applicant is advised that the process claims should be amended during prosecution either to maintain dependency on the product claims or to otherwise include the limitations of the product claims. Failure to do so may result in a loss of the right to rejoinder.

Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Information Disclosure Statement

Applicants' filing of information disclosures, filed on 05/13/2009, 07/25/2007 and 08/22/2006, are acknowledged. Those references considered have been initialed, while those missing references or having no date have been lined through.

Objections to the Specification

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code on page 13, last line; and page 23, line 12. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

The use of the trademarks "Genetyx-Win", have been noted in this application (See page 8, line 15). Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks. The Examiner suggests capitalizing each letter of the word or including a proper trademark symbol, such as ™ or © following the word.

Appropriate correction is required.

Claim Objections

Claim 4 is objected to because of the following informalities:

Claim 4 is objected to under 37 CFR 1.75(c) as being in improper form because it depends from a multiple dependent claim 3. See MPEP § 608.01(n). Accordingly, the claim has not been further treated on the merits.

Appropriate correction is required.

Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-3 and 10 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-3 and 10 recite the phrase, "a mutant *Bacillus* bacterium", which is unclear and indefinite. The term "mutant" is indefinite because it is a relative term when there is no reference to what is being regarded as a "wild-type" *Bacillus* bacterium. As such, it is unclear how one can distinguish "a mutant *Bacillus* bacterium" from any other naturally occurring *Bacillus* bacteria. Furthermore, the claims as written do not specifically point out any non-naturally occurring characteristics of the *Bacillus* bacterium which distinguish the *Bacillus* bacterium as a "mutant" (see below rejection under 35 U.S.C. § 101. The Examiner notes that the phrase, "a mutant *Bacillus* bacterium", is not defined in the specification. In the interest of advancing prosecution, the noted phrase is interpreted as any naturally or non-naturally occurring *Bacillus* bacterium.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-3 and 10 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

The claimed product and process, as written, does not sufficiently distinguish over the naturally occurring *Bacillus subtilis* bacterium and the process of replication in *Bacillus* bacterium, respectively. First, it is noted by the Examiner that the phrase "a mutant *Bacillus* bacterium" is interpreted as any naturally or non-naturally occurring *Bacillus* bacterium (see above rejection under 35 U.S.C. § 112 2nd paragraph for the claim interpretation). In light of this interpretation of the claims, Haldenwang (The Sigma Factors of *Bacillus subtilis*, Microbiological Reviews, Mar. 1995, p. 1-30) provides the evidence that a naturally occurring *Bacillus subtilis* bacterium comprises on its genome, DNA having promoter sequences, P1-P6, recognized and transcribed specifically during the sporulation stage, and a *sigA* gene, the promoter sequences being ligated to an upstream end of the *sigA* gene (see Figure 2 on page 5, and the section under "Regulation of the *sigA* operon" on page 5). Claim 2 is included in this rejection because Haldenwang teaches that a naturally occurring *Bacillus subtilis* bacterium comprises a promoter, P3, which is recognized and transcribed specifically during the sporulation stage as a promoter for expressing a *sigH* (σ^H) gene of *Bacillus subtilis* (see the section under "Regulation of the *sigA* operon" on page 5, especially

right column, lines 18-21). Furthermore, a method for constructing any naturally occurring *Bacillus* bacterium, characterized by constructing, on the genome of a bacterium belonging to the genus *Bacillus*, DNA having a promoter sequence recognized and transcribed specifically during the sporulation stage, and a *sigA* gene, the promoter sequence being ligated to an upstream end of the *sigA* gene, as recited in claim 10, does not sufficiently distinguish over the naturally occurring process of replication of *Bacillus subtilis* bacterium, which comprises on its genome, DNA having promoter sequences, P1-P6, recognized and transcribed specifically during the sporulation stage, and a *sigA* gene, the promoter sequences being ligated to an upstream end of the *sigA* gene. As such, claims do not particularly point out any non-naturally occurring differences between the claimed product/process, and the naturally occurring product/process. In the absence of "the hand of man", the naturally occurring products/processes are considered non-statutory subject matter. See Diamond v. Chakrabarty, 447 U.S. 303, 206, USPQ 193 (1980) and M.P.E.P. 2105.

Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3 and 10 are rejected under 35 U.S.C. § 112, first paragraph, written description, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to

reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant claims are directed to a genus of any naturally or non-naturally occurring *Bacillus* bacteria comprising, on the genome or plasmid thereof, DNA having *any promoter sequence recognized and transcribed specifically during the sporulation stage*, and a *sigA* gene or a gene equivalent thereto, the promoter sequence being ligated to an upstream end of the *sigA* gene or a gene equivalent thereto, optionally wherein the promoter sequence specifically recognized and transcribed during the sporulation stage is *any promoter sequence* for expressing a *sigH* gene of Bacillus subtilis or *any sequence equivalent thereto* and/or *any promoter sequence* for expressing a *spoIIA* operon of *Bacillus subtilis* or *any sequence equivalent thereto*; and a method for constructing any naturally or non-naturally occurring Bacillus bacterium, characterized by constructing, on the genome or a plasmid of a bacterium belonging to the genus Bacillus, DNA having *any promoter sequence recognized and transcribed specifically during the sporulation stage*, and a sigA gene or a gene equivalent thereto, the promoter sequence being ligated to an upstream end of the sigA gene or a gene equivalent thereto (italicized for added emphasis, see above rejection under 35 U.S.C. § 112 2nd paragraph for the claim interpretation).

To satisfy the written description aspect of 35 U.S.C. § 112, first paragraph, for a claimed genus of [compositions or methods], it must be clear that: (1) the identifying characteristics of the claimed [compositions or methods] have been disclosed, e.g., structure, physical and/or chemical characteristics, functional characteristics when

coupled with a known or disclosed correlation between function and structure, or a combination of these; and (2) a representative number of species within the genus must be disclosed.

The Court of Appeals for the Federal Circuit has recently held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as be structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." University of California v. Eli Lilly and Co., 1997 U.S. App. LEXIS 18221, at *23, quoting Fiers v. Revel, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original). To fully describe a genus of genetic material, which is a chemical compound, applicants must (1) fully describe at least one species of the claimed genus sufficient to represent said genus whereby a skilled artisan, in view of the prior art, could predict the structure of other species encompassed by the claimed genus and (2) identify the common characteristics of the claimed molecules, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these (paraphrased from Enzo Biochemical Inc. v. Gen-Probe Inc. (CAFC (2002) 63 USPQ2d 1609).

University of Rochester v. G.D. Searle & Co. (69 USPQ2d 1886 (2004)) specifically points to the applicability of both Lily and Enzo Biochemical to methods of using products, wherein said products lack adequate written description. While in University of Rochester v. G.D. Searle & Co. the methods were held to lack written description because not a single example of the product used in the claimed methods

was described, the same analysis applies wherein the product, used in the claimed methods, must have adequate written description as noted from Enzo Biochemical (see above).

First, it is noted by the Examiner that the phrase, "*sigA* gene" and "a gene equivalent thereto", have been interpreted as "a gene encoding an amino acid sequence represented by SEQ ID NO: 1", and "a gene encoding an amino acid sequence having a homology of 70% or more to the amino acid sequence represented by SEQ ID NO: 1", respectively, according to page 9, paragraph [0019] of the specification. In addition, the phrase, "a mutant *Bacillus* bacterium", has been interpreted as any naturally or non-naturally occurring *Bacillus* bacterium (see above rejection under 35 U.S.C. § 112 2nd paragraph for the claim interpretation). Moreover, the phrase, "a sequence equivalent thereto" as recited in claim 2, has been interpreted as referring back to "a promoter sequence". As such, the scope of the claims encompass a genus of [i] any naturally or non-naturally occurring *Bacillus* bacteria comprising, on the genome or plasmid thereof, DNA having *any promoter sequence recognized and transcribed specifically during the sporulation stage*, and a *sigA* gene or a gene equivalent thereto, the promoter sequence being ligated to an upstream end of the *sigA* gene or a gene equivalent thereto, optionally wherein the promoter sequence specifically recognized and transcribed during the sporulation stage is *any promoter sequence* for expressing a *sigH* gene of *Bacillus subtilis* or *any sequence equivalent thereto* and/or *any promoter sequence* for expressing a *spoIIA* operon of *Bacillus subtilis* or *any sequence equivalent thereto*; and [ii] a method for constructing any

naturally or non-naturally occurring *Bacillus* bacterium, characterized by constructing, on the genome or a plasmid of a bacterium belonging to the genus *Bacillus*, DNA having *any promoter sequence recognized and transcribed specifically during the sporulation stage*, and a *sigA* gene or a gene equivalent thereto, the promoter sequence being ligated to an upstream end of the *sigA* gene or a gene equivalent thereto (italicized for added emphasis).

However, given [A] the high level of unpredictability associated with predicting the function of a promoter sequence, i.e., being recognized and transcribed specifically during the sporulation stage of any naturally or non-naturally occurring *Bacillus* bacteria, based on its structure, i.e., any promoter sequence or any sequence equivalent thereto, or predicting the structure of a promoter sequence based on its function, [B] lack of structure-to-function correlation between [i] any promoter sequence or any sequence equivalent thereto (structure), and [ii] being recognized and transcribed specifically during the sporulation stage of any naturally or non-naturally occurring *Bacillus* bacteria (function), and [C] the limited disclosure of the specification which only discloses a few species, i.e., [1] a mutant *Bacillus* bacterium comprising, on its genome, DNA having a promoter for expressing the *sigH* gene, wherein said promoter is obtained from the use of primers as set forth in SEQ ID NO: 12 and 13 (1.1 kb fragment), which is ligated to an upstream end of the *sigA* structural gene obtained from the use of primers as set forth in SEQ ID NO: 8 and 9 (1.0 kb fragment), and the chloramphenicol-resistant gene obtained from the use of primers as set forth in SEQ ID NO: 14 and 15 (0.9 kb fragment), wherein said chloramphenicol-resistant gene was ligated, in a reverse

direction, downstream of the sigA structural gene according to pages 35-36 of the specification; and [2] a method for constructing said mutant *Bacillus* bacterium wherein said DNA was inserted into its genome via homologous recombination according to Example 2 on pages 37-38 of the specification, one of skill in the art would not have been able to recognize that the genus of any promoter sequence or any sequence equivalent thereto which can be recognized and transcribed specifically during the sporulation stage of any naturally or non-naturally occurring *Bacillus* bacteria, from those that lack such functions.

Given the lack of additional representative species of the genus of [i] any naturally or non-naturally occurring *Bacillus* bacteria comprising, on the genome or plasmid thereof, DNA having *any promoter sequence recognized and transcribed specifically during the sporulation stage*, and a *sigA* gene or a gene equivalent thereto, the promoter sequence being ligated to an upstream end of the *sigA* gene or a gene equivalent thereto, optionally wherein the promoter sequence specifically recognized and transcribed during the sporulation stage is *any promoter sequence* for expressing a *sigH* gene of Bacillus subtilis or *any sequence equivalent thereto* and/or *any promoter sequence* for expressing a *spoIIA* operon of *Bacillus subtilis* or *any sequence equivalent thereto*; and [ii] a method for constructing any naturally or non-naturally occurring Bacillus bacterium, characterized by constructing, on the genome or a plasmid of a bacterium belonging to the genus Bacillus, DNA having *any promoter sequence recognized and transcribed specifically during the sporulation stage*, and a sigA gene or a gene equivalent thereto, the promoter sequence being ligated to an upstream end of

the sigA gene or a gene equivalent thereto, as encompassed by the claims, Applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claims 1-3 and 10 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for [1] a mutant *Bacillus* bacterium comprising, on its genome, DNA having a promoter for expressing the *sigH* gene, wherein said promoter is obtained from the use of primers as set forth in SEQ ID NO: 12 and 13 (1.1 kb fragment), which is ligated to an upstream end of the *sigA* structural gene obtained from the use of primers as set forth in SEQ ID NO: 8 and 9 (1.0 kb fragment), and the chloramphenicol-resistant gene obtained from the use of primers as set forth in SEQ ID NO: 14 and 15 (0.9 kb fragment), wherein said chloramphenicol-resistant gene was ligated, in a reverse direction, downstream of the sigA structural gene according to pages 35-36 of the specification; and [2] a method for constructing said mutant *Bacillus* bacterium wherein said DNA was inserted into its genome via homologous recombination according to Example 2 on pages 37-38 of the specification, does not reasonably provide enablement for any naturally or non-naturally occurring *Bacillus* bacteria comprising, on the genome or plasmid thereof, DNA having *any promoter*

sequence recognized and transcribed specifically during the sporulation stage, and a *sigA* gene or a gene equivalent thereto, the promoter sequence being ligated to an upstream end of the *sigA* gene or a gene equivalent thereto, optionally wherein the promoter sequence specifically recognized and transcribed during the sporulation stage is *any promoter sequence* for expressing a *sigH* gene of Bacillus subtilis or *any sequence equivalent thereto* and/or *any promoter sequence* for expressing a *spoIIA* operon of *Bacillus subtilis* or *any sequence equivalent thereto*; and a method for constructing any naturally or non-naturally occurring Bacillus bacterium, characterized by constructing, on the genome or a plasmid of a bacterium belonging to the genus Bacillus, DNA having *any promoter sequence recognized and transcribed specifically during the sporulation stage*, and a sigA gene or a gene equivalent thereto, the promoter sequence being ligated to an upstream end of the sigA gene or a gene equivalent thereto (italicized for added emphasis, see above rejection under 35 U.S.C. § 112 2nd paragraph for the claim interpretation). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731, 737, 8 USPQ2nd 1400 (Fed. Cir. 1988)) as follows: 1) quantity of experimentation necessary, 2) the amount of direction or guidance presented, 3) the presence and absence of working examples, 4) the nature of the invention, 5) the state of prior art, 6) the relative skill of those in the art, 7) the predictability or unpredictability of the art, and 8) the breath of the claims. The

factors which have lead the Examiner to conclude that the specification fails to teach how to make and/or use the claimed invention without undue experimentation, are addressed in detail below.

The breath of the claims. First, it is noted by the Examiner that the phrase, "*sigA* gene" and "a gene equivalent thereto", have been interpreted as "a gene encoding an amino acid sequence represented by SEQ ID NO: 1", and "a gene encoding an amino acid sequence having a homology of 70% or more to the amino acid sequence represented by SEQ ID NO: 1", respectively, according to page 9, paragraph [0019] of the specification. In addition, the phrase, "a mutant *Bacillus* bacterium", has been interpreted as any naturally or non-naturally occurring *Bacillus* bacterium (see above rejection under 35 U.S.C. § 112 2nd paragraph for the claim interpretation). Moreover, the phrase, "a sequence equivalent thereto" as recited in claim 2, has been interpreted as referring back to "a promoter sequence". As such, the scope of the claims encompass a genus of any naturally or non-naturally occurring *Bacillus* bacteria comprising, on the genome or plasmid thereof, DNA having *any promoter sequence recognized and transcribed specifically during the sporulation stage*, and a *sigA* gene or a gene encoding an amino acid sequence having a homology of 70% or more to the amino acid sequence represented by SEQ ID NO: 1, the promoter sequence being ligated to an upstream end of the *sigA* gene or a gene equivalent thereto, optionally wherein the promoter sequence specifically recognized and transcribed during the sporulation stage is *any promoter sequence* for expressing a *sigH* gene of *Bacillus subtilis* or *any sequence equivalent thereto* and/or *any promoter sequence* for

expressing a *spoIIA* operon of *Bacillus subtilis* or *any sequence equivalent thereto*; and a method for constructing any naturally or non-naturally occurring *Bacillus* bacterium, characterized by constructing, on the genome or a plasmid of a bacterium belonging to the genus *Bacillus*, DNA having *any promoter sequence recognized and transcribed specifically during the sporulation stage*, and a *sigA* gene or a gene equivalent thereto, the promoter sequence being ligated to an upstream end of the *sigA* gene or a gene equivalent thereto (italicized for added emphasis). The enablement provided is not commensurate in scope with the claims due to the extremely large number of promoter sequences and sequences equivalent thereto of unknown structure encompassed by the claims. In the instant case, the specification enables a few species, i.e., [1] a mutant *Bacillus* bacterium comprising, on its genome, DNA having a promoter for expressing the *sigH* gene, wherein said promoter is obtained from the use of primers as set forth in SEQ ID NO: 12 and 13 (1.1 kb fragment), which is ligated to an upstream end of the *sigA* structural gene obtained from the use of primers as set forth in SEQ ID NO: 8 and 9 (1.0 kb fragment), and the chloramphenicol-resistant gene obtained from the use of primers as set forth in SEQ ID NO: 14 and 15 (0.9 kb fragment), wherein said chloramphenicol-resistant gene was ligated, in a reverse direction, downstream of the sigA structural gene according to pages 35-36 of the specification; and [2] a method for constructing said mutant *Bacillus* bacterium wherein said DNA was inserted into its genome via homologous recombination according to Example 2 on pages 37-38 of the specification.

The amount of direction or guidance presented and the existence of working examples. The specification discloses [1] a mutant *Bacillus* bacterium comprising, on its genome, DNA having a promoter for expressing the *sigH* gene, wherein said promoter is obtained from the use of primers as set forth in SEQ ID NO: 12 and 13 (1.1 kb fragment), which is ligated to an upstream end of the *sigA* structural gene obtained from the use of primers as set forth in SEQ ID NO: 8 and 9 (1.0 kb fragment), and the chloramphenicol-resistant gene obtained from the use of primers as set forth in SEQ ID NO: 14 and 15 (0.9 kb fragment), wherein said chloramphenicol-resistant gene was ligated, in a reverse direction, downstream of the sigA structural gene according to pages 35-36 of the specification; and [2] a method for constructing said mutant *Bacillus* bacterium wherein said DNA was inserted into its genome via homologous recombination according to Example 2 on pages 37-38 of the specification as working examples. However, the specification fails to provide any clue as to the structural elements required in any promoter sequence or any sequence equivalent thereto which can be recognized and transcribed specifically during the sporulation stage of any naturally or non-naturally occurring *Bacillus* bacteria, or which are the structural elements in any promoter sequence or any sequence equivalent thereto which are essential for any promoter sequence or any sequence equivalent thereto to display a desired function, i.e., being recognized and transcribed specifically during the sporulation stage of any naturally or non-naturally occurring *Bacillus* bacteria. No correlation between structure and function has been presented.

The state of prior art, the relative skill of those in the art, and the predictability or unpredictability of the art. The nucleic acid sequence of a promoter determines its structural and functional properties. In addition, the art teaches that the trans-acting regulators and local DNA topology all contribute to the functional properties of a promoter sequence (see the reference of Hengge-Aronis, Current Opinion in Microbiology, 2002, 5:591–595, especially pages 591-553). While the art discloses several promoters, neither the specification nor the art provides a direct correlation between structure of a promoter sequence or sequence equivalent thereto and function, i.e., being recognized and transcribed specifically during the sporulation stage of any naturally or non-naturally occurring *Bacillus* bacteria, such that one of skill in the art can envision the structure of any promoter sequence or any sequence equivalent thereto which can be recognized and transcribed specifically during the sporulation stage of any naturally or non-naturally occurring *Bacillus* bacteria. In addition, the art does not provide any teaching or guidance as to (1) which changes can be made to any promoter sequence such that the resulting variant or any sequence equivalent thereto would display a desired biological function, i.e., being recognized and transcribed specifically during the sporulation stage of any naturally or non-naturally occurring *Bacillus* bacteria, or (2) the general tolerance of a desired biological function, i.e., being recognized and transcribed specifically during the sporulation stage of any naturally or non-naturally occurring *Bacillus* bacteria, to structural modifications and the extent of such tolerance. The art clearly teaches that modification of nucleic acid sequence of any promoter sequence or any sequence equivalent thereto to obtain the desired biological function

without any guidance/knowledge, as to which nucleic acids in a promoter or a sequence equivalent thereto are tolerant of modification and which ones are conserved, is highly unpredictable. At the time of the invention there was a high level of unpredictability associated with altering a promoter sequence or a sequence equivalent thereto with an expectation that the resulting sequence will maintain the desired biological activity. In support of this notion, Hengge-Aronis teaches that even small nucleic acid changes in a promoter sequence result in functional changes, i.e., selectivity of a promoter changes from $E\sigma^{70}$ to $E\sigma^{S}$ (see page 592, Figure 1, and under "Promoter sequence elements that contribute to $E\sigma^{S}$ selectivity on pages 591-592).

The quantity of experimentation required to practice the claimed invention based on the teachings of the specification. While methods of making a promoter sequence were known in the art at the time of the invention, it was not routine in the art to screen by a trial and error process for all promoter sequences and all sequences equivalent thereto having desired biological function, i.e., being recognized and transcribed specifically during the sporulation stage of any naturally or non-naturally occurring *Bacillus* bacteria. In the absence of (1) a rational and predictable scheme for modifying any residue in any promoter sequence or any sequence equivalent thereto such that the resulting variant would maintain the desired biological function, i.e., being recognized and transcribed specifically during the sporulation stage of any naturally or non-naturally occurring *Bacillus* bacteria, and/or (2) a correlation between structure and function, one of skill in the art would have to test an essentially infinite number of all possible promoter sequences and all possible sequences equivalent thereto to

determine which ones have the desired biological activity, i.e., being recognized and transcribed specifically during the sporulation stage of any naturally or non-naturally occurring *Bacillus* bacteria.

Therefore, taking into consideration the extremely broad scope of the claims, the lack of guidance, the amount of information provided, the lack of knowledge about a correlation between structure and the desired function, and the high degree of unpredictability of the prior art in regard to structural changes and their effect on function, one of ordinary skill in the art would have to go through the burden of undue experimentation in order to practice the claimed invention. Thus, Applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the invention in a manner reasonably correlated with the scope of the claims.

Claim Rejections - 35 U.S.C. § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3 and 10 are rejected under 35 U.S.C. § 102(b) as being anticipated by Hicks et al. (Altering the level and regulation of the major sigma subunit of RNA polymerase affects gene expression and development in *Bacillus subtilis*, Molecular Microbiology, 1996, 20(1), pp. 201-212) in view of an evidentiary reference of

Haldenwang (The Sigma Factors of *Bacillus subtilis*, Microbiological Reviews, Mar. 1995, p. 1-30).

The instant claims are drawn to a naturally or non-naturally occurring *Bacillus* bacteria comprising, on the genome or plasmid thereof, DNA having a promoter sequence recognized and transcribed specifically during the sporulation stage, and a *sigA* gene or a gene equivalent thereto, the promoter sequence being ligated to an upstream end of the *sigA* gene or a gene equivalent thereto, optionally wherein the promoter sequence specifically recognized and transcribed during the sporulation stage is a promoter sequence for expressing a *sigH* gene of Bacillus subtilis or a sequence equivalent thereto and/or a promoter sequence for expressing a *spoIIA* operon of *Bacillus subtilis* or a sequence equivalent thereto; and a method for constructing any naturally or non-naturally occurring Bacillus bacterium, characterized by constructing, on the genome or a plasmid of a bacterium belonging to the genus Bacillus, DNA having a promoter sequence recognized and transcribed specifically during the sporulation stage, and a sigA gene or a gene equivalent thereto, the promoter sequence being ligated to an upstream end of the sigA gene or a gene equivalent thereto (see above rejection under 35 U.S.C. § 112 2nd paragraph for the claim interpretation).

Hicks et al. teach a wild-type *Bacillus subtilis* strains (JH642b and KH441c) and mutant *Bacillus subtilis* strains (KH311b and KH516c), wherein said mutant strains comprise, on their genome or plasmid, DNA having IPTG-inducible promoter Pspac recognized and transcribed specifically during the sporulation stage, and a *rpoD* gene (also known as *sigA*) gene, the promoter sequences being ligated to an upstream end

of the *sigA* gene (see Table 2 on page 205, and under Experimental procedures on pages 208-210), thereby anticipating Claims 1 and 3. It is noted that the wild-type *Bacillus subtilis* strains (JH642b and KH441c) also meet the limitations of Claims 1 and 3 because the evidentiary reference of Haldenwang teaches that a naturally occurring *Bacillus subtilis* bacterium comprises on its genome, DNA having promoter sequences, P1-P6, recognized and transcribed specifically during the sporulation stage, and a *sigA* gene, the promoter sequences being ligated to an upstream end of the *sigA* gene (see Figure 2 on page 5, and the section under "Regulation of the *sigA* operon" on page 5). Claim 2 is included in this rejection because Hicks et al. teach that P3 and P4 and the promoter sequences upstream of *sigH* (noted as σ^H), which are recognized and transcribed specifically during first 2 hours of sporulation (see Figure1 on page 202, and its legend). Claim 10 is included in the rejection because Hicks et al. teach a method for growing/replicating said wild-type *Bacillus subtilis* strains (JH642b and KH441c) and mutant *Bacillus subtilis* strains (KH311b and KH516c) in LB media (see under "Media" on page 208, right column), which meets the limitation of "a method for constructing any naturally or non-naturally occurring Bacillus bacterium, characterized by constructing, on the genome or a plasmid of a bacterium belonging to the genus Bacillus, DNA having a promoter sequence recognized and transcribed specifically during the sporulation stage, and a sigA gene or a gene equivalent thereto, the promoter sequence being ligated to an upstream end of the sigA gene or a gene equivalent thereto" as recited in Claim 10. Therefore, teachings of Haldenwang anticipate Claims 1-3 and 10.

Conclusion

Claims 1-3 and 10 are rejected and Claim 4 is objected to for the reasons as stated above. Applicants must respond to the objections/rejections in this Office action to be fully responsive in prosecution.

The instant Office action is non-final.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jae W. Lee whose telephone number is 571-272-9949. The examiner can normally be reached on M-F between 9:00-6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath Rao can be reached on 571-272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/JAE W LEE/
Examiner, Art Unit 1656